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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,134	04/03/2001	David Wallach	WALLACH=16A	2547

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EXAMINER

DAVIS, MINH TAM B

ART UNIT PAPER NUMBER

1642

DATE MAILED: 07/03/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/824,134

Applicant(s)

WALLACH ET AL.

Examiner

MINH-TAM DAVIS

Art Unit

1642

-- The MAILING DATE of this c mmunicati n appears n the cover sheet with the c rrespondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02/24/03, 03/26/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 and 11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-7, 11 are examined in the instant application.

INFORMATION DISCLOSURE STATEMENT

It is noted that although the PTO-1449 submitted on 04/03/01 is in the file of the instant application, the rest of the information disclosure statement of 04/03/01 is missing.

PRIORITY DATE

The submission of the priority foreign applications ISREAL 112022, ISREAL 112692 and ISREAL 114615 in paper No:8 of 04/01/03 is acknowledged. After review and reconsideration, the priority date of the instant application is determined to be 02/19/95, the filing date of the application ISREAL 112692, because the HF1 (MORT-1) clone in figure 5 of the previous application ISREAL 112022, filed on 12/15/94 is different from the HF1 (MORT-1) clone in figure 8 of the application ISREAL 112692.

REJECTION UNDER 35 USC 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement

thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1, and dependent claims 2-7, 11 are rejected under 35 USC 101 because the claims are directed to non-statutory subject matter.

The DNA molecule as claimed has the same characteristics and utility as a polypeptide found naturally and therefore do not constitute patentable subject matter. In the absence of the hand of man, the naturally occurring polypeptide is considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Amendment of the claims to recite " an isolated DNA molecule" is suggested to overcome this rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 1(2), 2-7, 11 remain rejected under 35 USC 112, first paragraph pertaining to lack of clear written description for reasons already of record in paper No: 7.

Applicant argues that whether or not the function of binding to FAS-IC is merely a physical property or is required for cell death is irrelevant. Applicant argues that the claims only require the property of binding to FAS-IC, and this property is sufficient to establish utility for the protein, e.g. it can be used to isolate FAS-IC by affinity chromatography. Applicant argues that thus this physical property is sufficient to establish utility for the DNA of the present invention, and it is irrelevant whether or not

the additional properties of cell death or activation of FAS ligand receptor are adequately establish.

Concerning the scope of the claimed analog, Applicant argues that similar to the example and analysis of the Revised Interim Written description Guidelines training materials, the procedure for determining variants by hybridization of moderate stringency is conventional in the art, and the single species disclosed is representative of the genus, because all members have at least the specified amount of structural identity with the reference compound, and because of the presence of an assay that Applicant has provided for identifying all of the compounds having the specified amount of structural identity that are capable of specified activity, in this case binding to FAS-IC.

Applicant concludes that thus the single disclosed species is representative of the genus, and the claimed invention meet the written description requirement.

Applicant's arguments in paper No: 9 have been considered but are found not to be persuasive for the following reasons:

Concerning utility for the binding to FAS-IC, it is noted that this is not a utility rejection.

Further, binding to the FAS ligand receptor is only a physical property, and not a function of the Mort-1 protein encoded by the claimed polynucleotide , because it is not clear whether cell death is due to the activation of FAS ligand receptor by MORT-1 protein or due to the expression of p55-IC in the transfected cells, and because it has not been shown that binding alone by the MORT-1 protein to the FAS ligand receptor is sufficient for the activation of FAS ligand receptor. In other words, binding to the FAS

ligand receptor, via the "death domain" of the FAS ligand receptor, which is located within the intracellular domain of the FAS ligand receptor, is only a physical property and not a function of the Mort-1 protein.

Moreover, the claim 1(2) as written states that it is the Mort-1 protein that binds to FAS-IC, but not the analogue. Given this, none of the claim 1(2) and dependent claims 2-7, 11 recite sufficient structure or function to meet the written description requirement.

Thus the claimed encompass unrelated sequences with undisclosed structure and function.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

1. Claims 1-7, 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cDNA sequence encoding the MORT-1 protein of SEQ ID NO:2, does not reasonably provide enablement for sequence encoding an analog of the MORT-1 protein of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-7, 11 are drawn to a "DNA" sequence encoding the amino acid sequence of SEQ ID NO:2, or an analog thereof, which binds to the intracellular domain of the FAS ligand receptor (FAS-IC), and is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions, or a fragment thereof, which binds to FAS-IC, a vector comprising said DNA sequence, host cells transformed

with said vector, and a method for producing a polypeptide which binds to FAS-IC, using said host cells.

Claims 1-7, 11 encompass a "genomic DNA" sequence encoding the amino acid sequence of SEQ ID NO:2, or an analog thereof, which binds to the intracellular domain of the FAS ligand receptor (FAS-IC), and is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions, or a fragment thereof, which binds to FAS-IC, a vector comprising said DNA sequence, host cells transformed with said vector, and a method for producing a polypeptide which binds to FAS-IC, using said host cells.

The specification discloses isolation of MORT-1 cDNA inserts of SEQ ID NO:1 (p.33, second paragraph, figure 4 legend).

One cannot extrapolate the teaching in the specification to the claims. The specification fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined (Harris et al. J. of The Am Society of Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and skilled in the art would therefore not recognize from the disclosure that applicant was in possession of the genus of nucleic acid, including genes, comprising SEQ ID NO: 1 or fragments thereof.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

2. If Applicant could overcome the above 112, first paragraph, claims 6-7 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "isolated" transformed host cells containing a vector containing the polynucleotide sequence of SEQ ID NO:1, does not reasonably provide enablement for transformed host cells containing a vector containing a DNA sequence encoding SEQ ID NO:2, an analog thereof, or a fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 6-7 are drawn to transformed host cells containing a vector containing a DNA sequence encoding SEQ ID NO:2, or an analog thereof, which binds to the intracellular domain of the FAS ligand receptor (FAS-IC), and is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions, or a fragment thereof, which binds to FAS-IC, a vector comprising said DNA sequence, and a method for producing a polypeptide which binds to FAS-IC, using said host cells.

Claims 6-7 encompass host cells transformed *in vivo* with a vector containing a DNA sequence encoding SEQ ID NO:2, or an analog thereof, which binds to the intracellular domain of the FAS ligand receptor (FAS-IC), and is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions, or a fragment thereof, which binds to FAS-IC. In other words, claims 6-7 encompass gene therapy, using the claimed vector.

The specification contemplates a method for modulating the FAS-R ligand effect on cells carrying a FAS-R, or treating tumor cells or HIV-infected cells, comprising introducing into said cells a vector containing a DNA sequence encoding SEQ ID NO:2, or an analog thereof, or a fragment thereof (p.9, items (i), (ii) and (vii)). There is however no disclosed data concerning the results of said method.

One cannot extrapolate the teaching in the specification to the claims, because of the following reasons. The state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known

in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

3. If Applicant could overcome the above 112, first paragraph, claims 1-7, 11 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a cDNA sequence of SEQ ID NO:1, does not reasonably provide enablement for an analog of a DNA sequence encoding the amino acid sequence of SEQ ID NO:2, which binds to the intracellular domain of the FAS ligand receptor (FAS-IC), and is capable of "hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-7, 11 are drawn to a DNA sequence encoding the amino acid sequence of SEQ ID NO:2, or an analog thereof, which binds to the intracellular domain of the

FAS ligand receptor (FAS-IC), and is capable of "hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions", or a fragment thereof, which binds to FAS-IC, a vector comprising said DNA sequence, host cells transformed with said vector, and a method for producing a polypeptide which binds to FAS-IC, using said host cells.

Claims 1-7, 11 encompass unrelated sequences with unknown function encoding a polypeptide that shares with SEQ ID NO:2 a fragment that binds to FAS-IC.

Applicant has not enabled these types of modified DNAs in the specification.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. *Journal of Cell Biology*, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. *Molecular and Cell Biology*, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. *The Journal of Immunology*, 1989, 143(8): 2595-2601, and Gillies et al. *Human Antibodies and Hybridomas*, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to

be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Further, the claims encompass polynucleotides comprising non-disclosed nucleic acid sequences attached to polynucleotides that encode MORT-1 protein, that is polynucleotides that hybridize to said polynucleotides under moderately stringent conditions . When given the broadest reasonable interpretation, it would be expected that a substantial number of the hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with polynucleotides that encode MORT-1 protein.

In view of the above, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Application/Control Number: 09/824,134
Art Unit: 1642

Page 12

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.


SUSAN UNGAR, PH.D.
PRIMARY EXAMINER

MINH TAM DAVIS

June 30, 2003